REMARKS

A check for the fees for filing an RCE and for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A change of address for the undersigned accompanies this response.

Claims 2-15, 18-27, 30, 32, 33, 34, 36, 37, 40 and 42-51 are pending herein. Claims 13, 14, 32, 34, 36, 37, 40 and 42 are amended for clarity and to ensure proper dependence. Basis for the amendments can be found in the application as originally filed. Particular basis can be found for example at page 10 lines 1-5, which recite:

> These results demonstrate that activation of receptors that activate PI3K bypasses the requirement for αv integrins or, for adenovirus, CAR to promote virus entry. Receptor bypass was highly effective when cytokine or growth factors were activated in close proximity to bound virus particles.

See also, page 30, lines 1-5

> It is shown herein that advantage can be taken of the similarity in signaling processes elicited by cell surface receptors that activate PI3 kinases and the α_v integrin mediated viral internalization, providing the basis for the methods and vectors provided herein, which bypass Ad integrin interaction to facilitate gene delivery.

Claim 16, which is substantially redundant with claim 32, claim 33, which is substantially redundant with claim 32, and claim 41, which is substantially redundant with pending claims, are cancelled without prejudice or disclaimer. No new matter is added.

Claims 46-50, which correspond to claim 32 and dependent claims prior to amendment of claim 32 in the previous response, are added. Claims 45-50 include the recitation display of the bifunctional molecule bound to a penton component results in bypass of binding to α_v integrin. Upon review of the art and as discussed below, the art does not teach or suggest fiberless or fiber-containing adenovirus particles that display a bifunctional molecule so that α_v integrin interaction is bypassed.

THE REJECTION OF CLAIMS UNDER 35 U.S.C. §103

Claims 2-16, 18-27, 30, 32-34 and 36, 37, and 40-45 are rejected as being unpatentable over Sosnowski *et al.*, WO 98/40508, in view of Stewart *et al.*, EMBO J. 16:1189-1198 (1997), Von Seggern *et al.*, J. Virol. 73:1601-1608 (1999), and Wickham *et*

al., J. Virol. 70:6831-6836 (1996) because Sosnowski *et al.* allegedly teaches tropism modified adenoviral vectors complexed to bispecific molecules, Von Seggern *et al.*. allegedly teaches the use of fiberless adenovirus for vector retargeting, Wickham *et al.* allegedly teaches modifying adenoviral tropism with a bispecific antibody that binds to the penton base, and Stewart *et al.* allegedly teaches the DAV-1 antibody, which binds to the RGD motif in the penton base. The Examiner concludes that it would have been obvious to have modified the compounds of Sosnowski *et al.* with the fiberless adenovirus of Von Seggern *et al.*, the penton base-binding bispecific molecule of Wickham *et al.* and the DAV-1 antibody of Stewart *et al.* to form the claimed targeted delivery vector particles. This rejection is respectfully traversed.

The claims:

Adenovirus virus penton base proteins interact via their RGD motifs with α_v integrins on cell surface. This interaction promotes virus internalization, via a receptor-mediated endocytosis pathway, into clathrin-coated pits and endosomes. The interaction of adenovirus penton base protein with α_v integrins stimulates PI3K, is reported to be essential to viral entry. The clustering of the α_v integrins results in the formation of a cytoplasmic signaling complex involving at least three major components: cSRC, CAS and PI3K. This signaling complex is capable of further activation of the Rho family of small GTPases (Rac, CDC42) whose activation ultimately results in the reorganization of the actin cytoskeleton and enhanced virus internalization. This interaction (see, *e.g.*, Sosnowski *et al.*) is described in the art as critical for infectivity (see, *e.g.*, Sosnowski *et al.*, Von Seggern *et al.*, and Wickham *et al.*).

The instant application shows that interaction with α_v integrins is not required for targeted delivery and that alternative modes of activation of the PI3K signaling pathway, in the absence of α_v integrin interaction, can promote viral internalization into targeted cells. The application also confirms that fiber binding is not required for PI3K activation nor for viral internalization.

The vector particles with linked bifunctional molecules claimed in this application are designed to bypass α_v integrin interaction and to be used in methods that take advantage of the common cell signaling pathways initiated by interaction with surface proteins and

receptors that, upon ligand interaction, activate phosphatidylinositol 3 kinases (PI3K) or the phosphatidylinositol 3 (PI3) signaling pathway. The claimed particles contain a bifunctional molecule linked to the particle via penton, whereby interaction of penton in the particle with α_v integrins is inhibited or prevented, thus, bypassing α_v integrin interaction. The resulting particle is targeted to a receptor that activates the PI3 signaling pathway by virtue of the targeting agent in the bifunctional molecule but bypasses α_v integrin interaction The antibody in the bifunctional molecule specifically binds to penton or a component of penton in the capsid of the particle; and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway. In particular, the targeting agent binds to a cell surface protein that triggers phosphatidyl-inositol-3-OH kinase (PI3K) activation.

Thus, the claimed particles bypass binding to α_v integrin, since penton is unavailable for interaction with α_v integrin, and bind to a target that will trigger the PI3K pathway for internationalization of the particles. The bifunctional molecules are selected and designed to bind to cell surface receptors that activate PI3 kinases and the α_v integrin-mediated viral internalization and to penton to inhibit or prevent interaction of penton with α_v integrin. The claimed vectors, combinations and bifunctional molecules permit bypass of adenovirus α_v integrin interaction to facilitate gene delivery to targeted cells and tissues. The pending claims embody this.

Independent claim 32 is a directed to a targeted delivery vector particle. The particle is a fiberless adenovirus particle that has a bifunctional molecule linked to penton and that contains a fiberless adenovirus genome. Interaction of penton with the bifunctional molecule interferes with interaction of the resulting particle with α_v integrin. Interaction with α_v integrin is bypassed. The bifunctional molecule contains a penton-binding portion and a targeting agent that specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway so that upon binding of the particle that displays the bifunctional molecule, the PI3pathway is activated.

Independent claim 40 is directed to a fiberless adenoviral particle that includes a bifunctional molecule. The bifunctional molecules contains an antibody or antigen-binding portion and a targeting agent. The antibody or antigen-binding portion specifically binds to

penton to interfere with interaction of the vector particle with α_v integrin; and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway. The resulting particle does not interact with α_v integrin.

Independent claim 36 is directed to a combination that includes a fiberless adenoviral particle for delivering gene products to targeted cells; and a bifunctional molecule that when linked to the particle provides for bypass of α_v integrin interaction. The bifunctional molecules contains an antibody or antigen-binding portion and a targeting agent. The antibody or antigen-binding portion specifically binds to penton, and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway.

Independent claim 42 is directed to a bifunctional molecule that contains an antibody or antigen-binding portion and a targeting agent. The antibody or antigen-binding portion contains all or a portion of DAV-1 antibody. The antibody or portion thereof binds to a component of penton; and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway.

Independent claim 46 is directed to an adenoviral particle that includes a bifunctional molecule that contains an antibody or antigen-binding portion and a targeting agent that agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway. The antibody or antigen-binding portion interacts with penton to display the bifunctional molecule on the particle so that of the particle with α_v integrin is bypassed.

Differences between the teachings of the cited references and the instant claims

Sosnowski *et al.*

Sosnowski *et al.* teaches a general strategy for targeting viral vectors to cells expressing a specific receptor, in which a viral vector particle is linked to a ligand that binds to the specific receptor. One embodiment specifies that the linkage is effected by conjugating the ligand with an antibody that binds to a viral protein, such as a capsid component. (page 6, lines 25-26). Sosnowski *et al.* states that "any antibody that neutralizes or blocks a virus from targeting and binding to a cell" can be used. Sosnoswki *et al.* also teaches that binding is effected by fiber and the bifunctional molecules provided by Sosnowski *et al.* contain anti-knob protein antibodies conjugated to the FGF2 ligand (page 27, lines 17-19 and Examples

beginning at page 97). Sosnowski *et al.* further states that "[i]n various embodiments, the viral capsid protein is adenovirus fiber protein -for example, an adenovirus knob protein" (page 8, line 30 to page 9, line 1), and, furthermore, specifies that:

> [t]o be useful in retargeting adenovirus, the recombinant fusion protein must bind both the adenovirus knob as well as the cognate receptor. Thus these proteins are analyzed for their knob binding capacity in an ELISA." (page 32, lines 19-21).

The penton is mentioned only in the context of describing either the structure of the adenovirus (pages 23 and 24) or direct modification of a viral protein (fiber protein or penton base, see, e.g., page 25, line 24 to page 26, line 7) to produce modified viral vectors for use in conjunction with the conjugates taught by Sosnowski *et al.*

Sosnowski *et al.* does not teach or suggest bypassing α_v integrin interaction. Sosnowski *et al.* states (page 3) that:

> This invention utilizes recombinant constructs which confer the advantages of targeting via the fibroblast growth factor receptor upon adenovirus – in place of the adenovirus usual targeting via fiber protein – and thus represents an improved method for gene therapy as well as for therapeutic applications involving delivery of a gene.

Sosnowski *et al.* continues on page 25, lines 13-16:

> The Ad-derived viral vectors disclosed herein may be used to target and deliver genes into specific cells by incorporating the attachment sequence for other receptors (such as FGF*) onto the fiber p*rotein by recombinant DNA techniques or by immunological means, thus producing chimeric molecules or conjugates.(emphasis added)

Thus, Sosnowski *et al.* contemplates modification of binding of fiber to effect targeting. Sosnowski *et al.* does not contemplate modification of the interaction with α_v integrin. Sosnowski *et al.* mentions the penton only in the context of describing either the structure of the adenovirus or direct modification of a viral protein (fiber protein or penton base). Sosnowski *et al.* does not mention or suggest constructing a particle that bypasses α_v integrin interaction.

In fact Sosnowski *et al.* states (page 21, lines 5-10):

> In the context of adenovirus (Ad), it tends to bind to integrin receptors, which *is believed to be required for subsequent internalization of adenovirus into the host cell.* Adenoviruses attach to host-cell receptors via the penton fiber glyocoprotein and enter cells through the process of receptor mediated

> endocytosis mediated by the penton base. Ad apparently utilizes separate proteins for attachment and entry in a manner similar to enveloped human viruses. (emphasis added)

Thus, Sosnowski *et al.* teaches that integrin binding is required, thereby teaching away from bypassing α_v integrin interaction.

The reference in Sosnowski *et al.* to Wickham *et al.* does not suggest by-passing interaction with α_v integrin, which Sosnowski *et al.* teaches is required. As discussed below, Wickham *et al.* teaches modification of penton base to include a FLAG-epitope and the use of a bifunctional molecule that contains an anti-FLAG antibody and an α_v integrin binding protein to permit interaction of the resulting particle with α_v integrin. Hence α_v integrin interaction is no by-passed. Thus, Sosnowski *et al.* cannot be read to teach by-passing of α_v integrin interaction since 1) it teaches that it is required; and 2) in the only reference to a molecule that binds to a protein other than fiber, the cited reference includes an α_v binding protein as a targeting agent so that an Ad particle modified to display the bifunctional particle interacts with α_v integrin.

Sosnowski *et al.* does not teach bifunctional molecules containing an antibody that specifically binds to penton base. Sosnowski *et al.* does not teach or suggest preparation of a vector particle that does not bind to penton nor to CAR . Sosnowski *et al.* does not teach or suggest use of a bispecific molecule with a fiberless adenovirus particle. Sosnowski *et al.* also does not teach or suggest eliminating binding to α_v integrin and *instead* employing binding to another receptor that activates the PI3 signaling pathway. Sosnowski *et al.* retargets by changing the specificity of the fiber. Wickham *et al.* discussed in Sosnowski *et al.*, targets to α_v integrin.

The instantly claimed vector particles and bifunctional molecules, which contain an antibody that specifically binds to penton base and a targeting agent (ligand) that specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3K) signaling pathway, are designed to improve the specificity and efficiency of viral vector-mediated gene delivery to cells, including cells lacking αv integrin receptors by bypassing α_v integrin interaction. Sosnowki *et al.* does not teach or suggest bifunctional molecules and particles that are designed to circumvent α_v integrin interactions. Sosnowski *et al.* does not teach or

suggest any bifunctional molecules that specifically bind to and effect viral vector-mediated gene delivery in cells that lack integrin receptors.

Stewart *et al.*

Stewart *et al.* teaches the DAV-1 antibody, which binds to a linear epitope of the adenovirus penton base protein. Stewart *et al.* further teaches that binding of an Fab fragment of DAV-1 antibody to the RGD epitope of penton base blocks adenovirus infectivity, thereby suggesting that by-passing α_v integrin binding blocks Ad vector infectivity.

Also, Stewart *et al.* does not teach or suggest the use of the antibody in a bifunctional molecule or the use of the antibody in conjunction with an adenovirus particle to form a targeted delivery vector particle. Stewart *et al.* does not teach or suggest a vector particle that does not bind to α_v integrin nor the expression of a targeting agent on the particle to effect binding to a receptor that activates the PI3 signaling pathway. Hence Stewart *et al.* does not cure the deficiencies in the teachings of Sosnowski *et al.*

Von Seggern *et al.*

Von Seggern *et al.* teaches that Ad fiber protein largely determines tropism and construction of a fiberless mutant to assess the fiber null phenotype. Von Seggern *et al.* teaches vector retargeting by incorporating different fibers expressed by different packaging lines. Von Seggern *et al.* does not teach or suggest retargeting by bypassing the α_v integrin interaction. Instead, Von Seggern *et al.* teaches that fiberless adenovirus particles can infect monocytic cells via an *integrin-dependent pathway*; Von Seggern *et al.* does not suggest targeting a fiberless vector via an *integrin-**independent** pathway*..

Von Seggern *et al.* mentions that the fiberless virus in combination with packaging cell systems might be useful in vector retargeting, but intends for the fiberless mutant to be used to produce viruses with heterologous fibers (see, *e.g.*, page 1607, paragraph 2):

> Since any fiber in an AD5.βgal.ΔF is produced in *trans* by packaging cells, this system should simplify the use of fiber modifications in vector retargeting.

Thus, Von Seggern *et al.* does not teach or suggest elimination or bypassing of the α_v integrin pathway, but rather teaches that tropism is determined by Ad fiber and retargeting is effected by modifying fiber. Von Seggern *et al. does* not teach or suggest use of the fiberless

adenoviral particle in conjunction with a bifunctional molecule nor vector retargeting with a bifunctional molecule nor vector retargeting with a fiberless particle. Von Seggern *et al.* does not teach or suggest eliminating interaction with α_v integrins nor a vector particle that does not bind to α_v integrins, since Von Seggern *et al.* teaches that the fiberless particles infect cells via an integrin-dependent pathway. Hence Von Seggern *et al.* does not cure the deficiencies in the teachings of Sosnowski *et al.* and Stewart *et al.*

Wickham *et al.*

Wickham *et al.* teaches targeting adenovirus fiber-containing particles to α_v integrin by replacing the RGD binding motif in penton with another epitope and complexing the particle with a bispecific antibody that binds to the epitope and displays an antibody that binds to α_v integrin. In particular, Wickham *et al.* teaches replacing the RGD motif in penton with a FLAG peptide, and using a bispecific molecule containing a FLAG specific monoclonal antibody *chemically linked to a monoclonal antibody that binds to α_v integrin* to target the adenovirus to α_v integrin.

Hence, Wickham *et al.* is directed to **targeting vectors to α_v integrins**, which it states are "promising tissue-specific receptors for targeted gene therapy" (see page 6836, col. 2, paragraph 3). The antibody in the bifunctional molecule of Wickham *et al.* is an anti-α_v integrin; hence the bifunctional molecule of Wickham *et al.* binds to α_v integrin. Therefore, the particles of Wickham *et al.* do not bypass α_v integrin interaction nor does Wickham *et al.*, teach or suggest bypassing α_v integrin interaction.

Hence, in contrast to the instantly claimed particles, which are designed so that binding to α_v integrin via penton is bypassed, the adenovirus particles of Wickham *et al.*, are designed to bind to α_v integrin receptors. Wickham *et al.* does not teach a fiberless adenovirus particle nor a particle complexed with a bifunctional molecule that prevents or inhibits binding of penton to α_v integrin, since its bifunctional molecule is targeted to α_v integrins. Wickham *et al.* does not teach bypassing α_v integrin interaction and exploiting the PI3 signaling pathway for viral internalization by targeting viral particles to other receptors that activate the PI3 signaling pathway. Wickham is focused on exploiting the α_v integrins as receptors for targeted delivery of adenoviruses, whereas the instantly claimed particles are

designed so that binding to α_v integrin is inhibited. Thus, Wickham *et al.* does not cure the deficiencies in the teachings of Sosnowski *et al.*, Stewart *et al.* and Von Seggern *et al.*

The combination of teachings of Sosnowski *et al* , Stewart *et al.* , Von Seggern *et al.* and Wickham *et al.* does not result in the instantly claimed viral particles, combinations or bifunctional molecules av

The combination of teachings of fails to teach or suggest viral particles that are designed to bypass interaction with α_v integrins. None of Sosnowski *et al.*, Stewart *et al.*, Von Seggern *et al.*, or Wickham *et al.*, singly or in any combination thereof, teaches or suggests particles that bypass α_v integrin interaction. Sosnowski *et al.*, includes anti-integrin antibodies as possible ligands and teaches that α_v integrin interaction is required for viral internalization. Wickham employs anti-integrin antibodies for targeting to α_v integrin. Hence both references in fact teach away from elimination or bypass of α_v integrin interaction. Stewart *et al.* does not cure this deficiency. Stewart *et al.* teaches that binding of an Fab fragment of DAV-1 antibody to the RGD epitope of penton base blocks adenovirus infectivity, thereby suggesting that by-passing αv integrin binding blocks Ad vector infectivity. Similarly Von Seggern *et al.* does not cure the deficiencies in the teachings of any of Sosnowski *et al.*, Wickham *et al.* and Stewart *et al.*, singly or in any combination thereof. Von Seggern *et al.* states that α_v integrin interaction is required for infectivity

None of the cited references teaches or suggests bypassing α_v interaction.

Therefore, the combination of teachings does not teach or suggest any of the claimed combinations, particles of bifunctional molecules. Furthermore, the combination of teachings does not suggest the instantly claimed bifunctional molecules, since none suggests preparation of a bifunctional molecule that contains a DAV-1 antibody or portion thereof. Only Stewart *et al.*, mentions DAV-1; and it does not suggest including it in a bifunctional molecule. Sosnowski *et al.*, describes bifunctional molecules that bind to fiber, not to penton Wickham *et al.*, specifically teaches a bifunctional molecule that binds to α_v integrin and does not suggest a molecule designed to bypass such binding. None of Sosnowski *et al.*, Stewart *et al.*, or Von Seggern *et al.* suggest bypassing α_v integrin binding.

Therefore the combination of teachings of the cited references cannot result in any of the instantly claimed particles, combinations and bifunctional molecules.

Rebuttal to Examiner's comments

1. The Examiner states:

> Sosnowski *et al.* differs from the instant invention by not specifically teaching that the adenoviral vector particle is a fiberless adenoviral particle. As noted above, Sosnowski *et al.* does in fact teach using modified viruses would natural tropism has been completely ablated. Von Seggern *et al.* supplements Sosnowski *et al.* by teaching that a fiberless adenovirus particle which comprises a fiberless adenoviral genome loses its natural tropism for infecting epithelial cells (Von Seggern *et al.*, page 1603-1604). Von Seggern *et al.* further teaches that the fiberless virus should be useful for vector re-targeting (Von Seggern *et al.*, page 160l- 1602, bridging sentence). Thus, based on the, motivation for making modified adenoviral particles whose native tropism has been ablated and which have a new tropism derived from a targeting fusion protein comprising an antibody that binds to a viral capsid protein and FGF provided by Sosnowski *et al.* and the motivation provided by Von Seggern *et al.*. for using a fiberless adenoviral particle in vector re-targeting, it would have been prima facie obvious to the [ordinarily] skilled artisan at the time of filing to use the fiberless adenoviral vectors and particles taught by Von Seggern *et al.* in the methods of re-targeting viral particles using anti-capsid antibody/FGF targeting molecules taught by Sosnowski *et al.*

Applicant respectfully disagrees. Sosnowski *et al.* teaches that tropism can be fully ablated, but does not suggest elimination or by passing α_v integrin interaction. All modifications described in Sosnowski *et al.* are directed to modification of fiber, which is described as responsible for tropism. The only modified Ad virus particle in which a bifunctional molecule is displayed via interaction with other than fiber is by reference to Wickham *et al.*, which as discussed above does not teach or suggest bypassing α_v integrin interaction. None of the references, singly or in combination, that describe ablation of tropism of particles as requiring or including elimination of the interaction with α_v integrin. Sosnowski *et al.*, Von Seggern *et al.* and Wickham *et al.*, teach or suggest that this interaction is required. Stewart *et al.*, is silent on this issue.

Furthermore with respect to the claims directed to fiberless particles, contrary to the characterization of the teachings of Von Seggern *et al.* noted above, Von Seggern *et al.* does not teach or suggest that a fiberless particle can be used for re-targeting by bypassing α_v integrin interaction. Von Seggern *et al.*, specifically teaches that its fiberless particles employ the α_v integrin interaction for infectivity. The fiberless particle was employed solely

to demonstrate that this pathway is functional for such particles. Further, for retargeting, the fiberless adenoviruses are used essentially as scaffolds for addition of different fibers to the particles by producing them in particular packaging cell lines. Nowhere in Von Seggern *et al.* is there a teaching or suggestion to employ fiberless particles that bypass α_v integrin interaction.

2. The Examiner also states:

> Sosnowski *et al.* further differ from the instant invention in that Sosnowski *et al.*, does not teach a specific antibody which binds to the penton base of the capsid, or the DAV-1 antibody in particular. However, Sosnowski *et al.* does reference a prior art publication by Wickham *et al.* and suggests that the protein and particles described therein may be useful in the methods disclosed by Sosnowski *et al.* (Sosnowski *et al.* , page 26, lines 5-7). Wickham *et al.* teaches modifying adenoviral tropism by complexing the adenoviral particle with a bispecific antibody that binds to a modified penton base on the viral particle and to integrin on surface of target cells (Wickham *et al.*, page 6831). Thus, by specifically referencing Wickham *et al.*, Sosnowski *et al.* provides specific motivation for modifying viral tropism by using a fusion protein comprising an antibody that binds to the penton base. Therefore, based on specific motivation to look to the teachings of Wickham *et al.* provided by Sosnowski *et al.*, it would be prima facie obvious to the [ordinarily] skilled artisan at the time of filing to make and use a targeting molecule as taught by Sosnowski *et al.*, which comprises an antibody that targets the penton base, as taught by Wickham *et al.* and a cell surface targeting protein such as FGF with a reasonable expectation of success.

Applicant respectfully disagrees. A discussed above, Wickham *et al.*, describes modification of penton in include a FLAG epitope and a bi-functional molecule that binds to the epitope and also binds to α_v integrin. Therefore, modification of the adenovirus in accord with Wickham *et al.* does not result in the instantly claimed particles or bifunctional molecules. Since all of the instant claims require bypassing of α_v integrin interaction. Wickham *et al.*, teaches that α_v interaction is required for infectivity.

3. The Examiner states that Sosnowski *et al.* teaches that the "the antibody [in the bifunctional molecule] can be targeted to the penton base cites pages 23-24 and page 26, lines 5-7 of Sosnowski *et al.* A review of pages 23-24 does not reveal any discussion therein that the bifunctional molecule can contain an antibody that binds to penton or any component thereof. The noted text on page 26, lines 5-7, states that "for example, modified penton base

polypeptides, such as those described in Wickham *et al.*, (J. Virol. 70:6831-8 (1996)) may have therapeutic value. As discussed above, Wickham *et al.* teaches modification of penton to include an epitope to which an antibody binds and then inclusion of a molecule that binds to αv integrin as the targeted molecule. Accordingly, Wickham, and, thus, Sosnowski *et al.* do not teach or suggest by passing α_v integrin interaction. Sosnowski *et al.*, includes molecules that interact with α_v integrin as possible targeting agents and Wickham *et al.*, teaches construction and use of a bifunctional molecule that interacts with α_v integrin. Neither reference teaches or suggests bypassing αv integrin interaction. Stewart *et al.* teaches that α_v interaction is required for infectivity.

4. The Examiner urges that Sosnowski *et al.* teaches complete ablation of the native tropism of the particle and cites page 22, lines 18-22, pages 22-23, bridging paragraph, pages 26-27 and page 37. At none of the cited text does Sosnowski *et al.* teach bypassing α_v integrin interaction.. At page 22, the noted text states that tropism may be ablated, but there is no teaching in the application or the noted text that suggests bypassing αv interaction, and it certainly does not suggest employing a fiberless virus. All examples and discussion in Sosnowski *et al.* are directed to modifications of fiber for retargeting. There is only generic discussion of binding to capsid proteins. The description of modification of penton references Wickham *et al.*, which as discussed above, teaches modification of penton by insertion of a heterologous epitope and then targeting to α_v integrin with an anti- α_v monoclonal antibody. Hence, there is no teaching in Sosnowski *et al.* or in Wickham *et al.*, singly or in any combination thereof, to suggest eliminating or bypassing α_v integrin interaction.

THE REJECTION OF CLAIMS 13, 14, 33, 37 AND 40 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 13 and 14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite because the claims are allegedly unclear. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

It is respectfully submitted that the claims are not intended to recite a product-by-process. Reference to the sequence of nucleotides defines the sequence of amino acids. It is

respectfully submitted that amendment of claims 13 and 14 to recite that the particle includes an antibody having the specified sequence of amino acids obviates this ground of rejection.

Claims 33, 37 and 40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reasons discussed and addressed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks. It is respectfully submitted that cancellation of claim 33 herein renders this ground of rejection moot.

Claim 37 is allegedly lacks antecedent basis for the recitation of "delivery vector particle." It is respectfully submitted that amendment of claims 36 and 37 herein obviates this rejection. Claims 36 and 37 recite a "vector particle."

Claim 40 is rejected as having improper antecedent basis for "bifunctional molecule." It is respectfully submitted that claim 40 as amended herein is an independent claim, thereby by obviating this rejection.

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In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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